Cannabis-based Medicines Approved for Intractable Epilepsy

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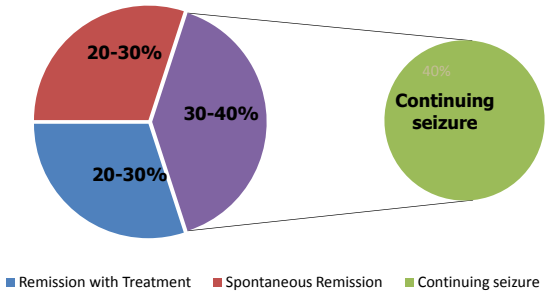
Definition Epilepsy : ILAE 2014

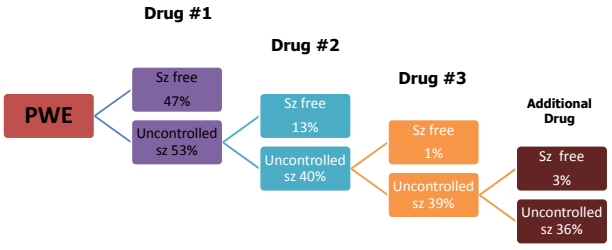
a. At least two unprovoked seizures occurring >24 hours apart
b. One unprovoked seizure and a probability for further seizures of at least 60%, occurring over the next 10 years or
c. The diagnosis of an epilepsy syndrome

Natural History of Newly-diagnosed epilepsy

Kwan P. et al, 2004



Seizure Control with Medication



PWE = people with epilepsy, sz = seizure

Kwan P, et al NEMJ, 2000

Refractory epilepsy definition

- Different terms may be used to describe these including: "uncontrolled," "intractable," "refractory," or "drug resistant."
- ILAE has proposed drug resistant epilepsy

Drug resistant epilepsy

- occurs when a person has failed to become (and stay) seizure free with adequate trials of **two** seizure medications (called AEDs).

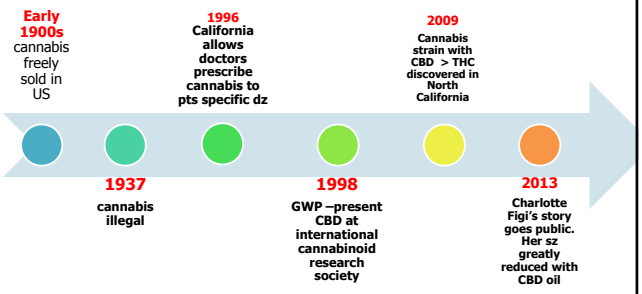
กัญชา Marijuana , Cannabis

- **Cannabinoids** refer to substances in cannabis
- **2 major ingredients in cannabinoids**
  - **Tetrahydrocannabinol (THC)** + **cannabidiol (CBD)**
- **Cannabis Sativa** has higher CBD:THC ratio than other strains (C. indica)

History : Epilepsy & cannabis

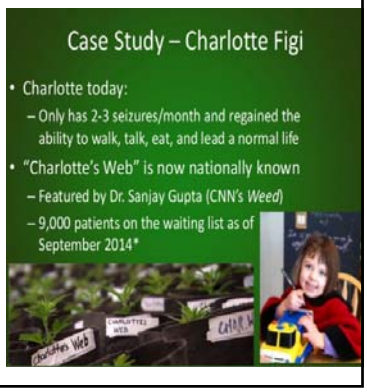
- Cannabis used as medical Rx for 1000++ years
- 2200 BCE. Sumaria 1st document use in epilepsy
- As late as 19th century, cannabis widely prescribed by western doctors : epilepsy, analgesia, hypnotic, etc
- Prohibition since early 20th century-> abandonment of cannabis as therapeutic agents
- Interest rekindled since 1980's : scientific development

Brief History of CBD



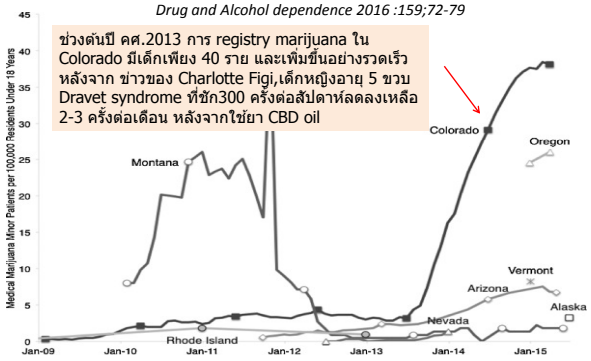
Severe epilepsy : cannabis

Dravet syndrome



Trends in registered medical marijuana participation across 13 US states and District of Columbia

Drug and Alcohol dependence 2016 :159;72-79



Dravet syndrome

- A rare genetic disorder that affects 1 in every 20,000–40,000 births
- Severe epilepsy , SCN1A-related seizure disorders
- Appears during the 1st year of life as frequent fever-related (febrile) seizures
- Other seizure types : typically myoclonus and status epilepticus
- Average age of death ~ 8 yo (ranges infancy -18 yrs of age)
  - Most common cause : sudden unexpected death in epilepsy SUDEP

Cannabidiol – seizure/epilepsy

- Preclinical studies suggest that cannabinoids (phytocannabinoids) have **anticonvulsant effects**
- Cannabidiol (CBD) and THC have shown **antiseizure effects** in both in vivo and in vitro models
- CBD does **not** produce euphoric or intrusive psychoactive side effects when used to treat seizures. (in **contrast** to THC)

Friedman D, et al. Epilepsy Behav 2017;70(Pt B):298-301.
dos Santos RG, et al. J Clin Pharm Ther 2015;40:135–43.
Friedman D, et al. N Engl J Med 2015;373:1048–58.

Possible Mechanism in Seizure Rx : CBD

- Via Endocannbinoid receptors? [CB(1)+CB(2)]
  - CBD **not** exert main effect through CB1R :may functⁿ as indirect @high level

    Ludanyi et al. J Neurosci 2008 , Romigi et al Epilepsia 2010
- Decreased presynaptic release of glutamate
- Inhibits adenosine reuptake
- Activates 5 HT 1A receptors
- Antagonism of G protein-coupled receptor 55
- Anti-inflammatory?
- Antioxidant?
- Modulation of mTOR pathway?
- ????

NEngl J Med 2015;373:1048-58
Epilepsy Behav 2017;70(Pt B):313-8
Pharmacol Res 2017;121: 213-8

Evidences : cannabinoid & epilepsy Rx

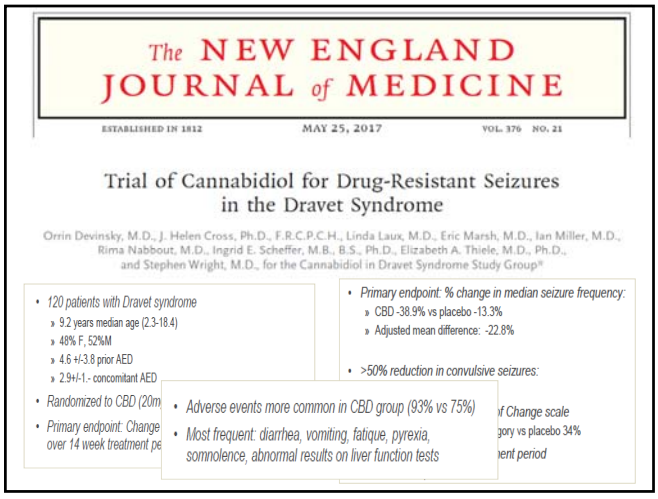
- Cannabinoids have been proposed as an adjunctive treatment for epilepsy and parents of children with epilepsy report using CBD products.
- There is evidence that cannabis -helpful in controlling seizures, esp for difficult to control conditions ie:
  - **Lennox-Gastaut syndrome (LGS) in children and adults**
  - **Dravet syndrome in children.**

Summarized RCT *Stockings E, et al, 2018*

Study	Design	Sample	Treatment	Pharma. grade	Outcomes measured
Ames and Crindland[30] *S Afr Med J 1986*	Randomised clinical trial	12 adults with frequent seizures not controlled by anticonvulsant therapy (drug-resistant epilepsy)	100 mg CBD or placebo sunflower oil 3 times a day for 1 week, then 2 times a day for 3 weeks	Not stated	Seizure reduction No sig difference
Cunha et al[25] *Pharmacology 1980*	Randomised, double-blind, placebo-controlled trial	15 adults (mean age=24; range 14–49; 26.7% male) with secondary generalised epilepsy (drug-resistant epilepsy)	100 mg CBD or placebo glucose capsule, taken orally 2–3 times per day, for 8–18 weeks	Not stated	Reported seizure improvement; self-reported subjective improvement SF : 4/7 vs 1/8 SR: 7/7 vs 2/8
Devinsky et al[26] *N Engl J Med 2017*	Randomised, double-blind, placebo-controlled trial	120 children and adolescents (mean age=9.8; range=2–18; 52% male) with Dravet syndrome (drug-resistant epilepsy)	20 mg/kg/day CBD or placebo, taken orally for 14 weeks, as an adjunctive treatment	Yes	Change in seizure frequency, caregiver global impression of change

Summarized RCT *Stockings E, et al, 2018*

Study	Design	Sample	Treatment	Pharma. grade	Outcomes measured
GW Pharmaceuticals[17] *GWPharmaceuticals 2017.*	Randomised, double-blind, placebo-controlled trial	225 patients (mean age=16; range=2–55) with Lennox-Gastaut syndrome (drug-resistant epilepsy)	i) 10 mg/kg/day CBD for 14 weeks		Yes
			ii) 20 mg/kg/day CBD for 14 weeks		Yes
Thiele et al[28] *The Lancet 2018*	Randomised, double-blind, placebo-controlled study	171 patients (mean age=15.4; range=2–45; 51.5% male) with Lennox-Gastaut syndrome (drug-resistant epilepsy)	20 mg/kg/day CBD or placebo, taken daily for 14 weeks, as an adjunctive treatment		Yes
Trembly and Sherman[19] *Kolympari,1990*	Double-blind, cross-over, placebo-controlled add-on trial	12 adults with incompletely controlled seizures (drug-resistant epilepsy)	100 mg CBD or placebo 3 times per day for 26 weeks		Not stated Some Sz Reduction No stat analysed



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 25, 2017 VOL. 376 NO. 21

Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D., Rima Nabbout, M.D., Ingrid E. Scheffer, M.B., B.S., Ph.D., Elizabeth A. Thiele, M.D., Ph.D., and Stephen Wright, M.D., for the Cannabidiol in Dravet Syndrome Study Group*

- 120 patients with Dravet syndrome
  - 9.2 years median age (2.3-18.4)
  - 48% F, 52%M
  - 4.6 +/-3.8 prior AED
  - 2.9+/-1.- concomitant AED
- Randomized to CBD (20m
- Primary endpoint: Change over 14 week treatment pe

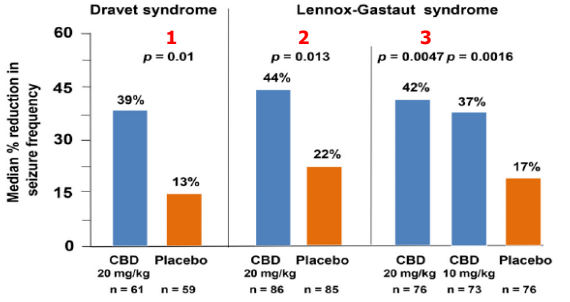
- Primary endpoint: % change in median seizure frequency:
  - CBD -38.9% vs placebo -13.3%
  - Adjusted mean difference: -22.8%
- >50% reduction in convulsive seizures:

- Adverse events more common in CBD group (93% vs 75%)
- Most frequent: diarrhea, vomiting, fatigue, pyrexia, somnolence, abnormal results on liver function tests

of Change scale
gory vs placebo 34%
ent period

Cannabidiol in Epilepsy , 3 RCT

Perruca E. Journal of Epilepsy Research Vol. 7, No. 2, 2017



1. Devinsky O, et al N Engl J Med 2017;376:2011-20 2. Mazurkiewicz-Beldzinska M, et al. IEC 2017, Epilepsia in press
3. Zuberi S, et al. IEC 2017, Epilepsia in press

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome

Orrin Devinsky, M.D., Anup D. Patel, M.D., J. Helen Cross, M.B., Ch.B., Ph.D., Vicente Villanueva, M.D., Ph.D., Elaine C. Wirrell, M.D., Michael Privitera, M.D., Sam M. Greenwood, Ph.D., Claire Roberts, Ph.D., Daniel Checketts, M.Sc., Kevan E. VanLandingham, M.D., Ph.D., and Sameer M. Zuberi, M.B., Ch.B., M.D., for the GWPCARE3 Study Group*

CONCLUSIONS

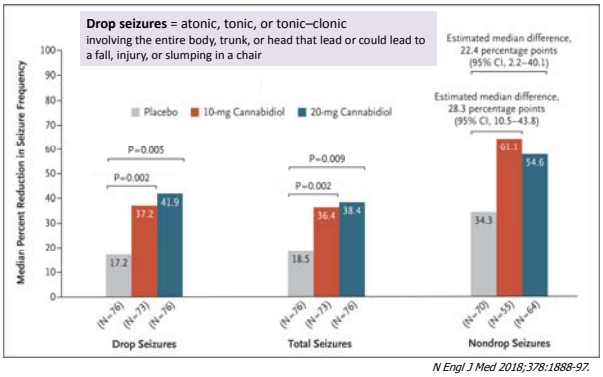
Among children and adults with the Lennox–Gastaut syndrome, the addition of cannabidiol at a dose of 10 mg or 20 mg per kilogram per day to a conventional antiepileptic regimen resulted in greater reductions in the frequency of drop seizures than placebo. Adverse events with cannabidiol included elevated liver aminotransferase concentrations.

N Engl J Med 2018;378:1888-97.

Lennox Gastaut Syndrome

- A rare and severe childhood epilepsy : start between 2-6 YO
- Incidence ~ 1:1,000,000 inhabitants per year
  - Estimated prevalence ~15/100,000.
  - 5-10% of epileptic pts, 1-4% of all childhood epilepsies.
- Frequent & several different kinds of seizures
  - Atonic, tonic, atypical absence, myoclonic
- Learning difficulties and developmental delays
- Mortality rate 3–7% in a mean FU period 8.5 to 9.7 Yrs
  - Death is often related to accidents

Lennox Gastaut Synd : CBD



N Engl J Med 2018;378:1888-97.

Adverse Effects

- Marijuana /cannabis has side effects included
  - Sleepiness, diarrhea, fatigue, & decreased appetite
- CBD: Serious Adverse Effects (SAE) any : 2.2%
  - Specific Treatment-related SAE (TSAEs) including status E , convulsion, hepatoxicity, pneumonia and death
- CBD has interactions with some AEDs (clobazam, carbamazepine, phenytoin, etc)

CBD: Adverse effects

Perruca E. Journal of Epilepsy Research Vol. 7, No. 2, 2017

RCT	Mazurkiewicz-Beldzinska M, et al 2017	Zuberi S, et al 2017
CBD (mkd)	20 vs placebo	20 vs 10 vs placebo
Concomitant AED	94% multiple AEDs; most common CLB 49%, VPA40%, LTG 37%	Median 3 concomitant AEDs
Adverse events (AE)	86% vs 69%	94% vs 84% vs 72%
Most common AE	diarrhea, somnolence, pyrexia, decreased appetite, vomiting	somnolence & decreased appetite.
TSAEs	9 vs 1	5 vs 2 vs no pts
Details	Increase transaminases mostly in pts on VPA and all resolved	Some elevations in transaminases were seen

CBD : THC 20:1 ratio Israel Experience

- Retrospective study of 74 pts (age 1-18 yo)
- Intractable epilepsy resistant > 7 AEDs
- CBD:THC ratio 20:1 dissolved in olive oil dose 1-20mkd
- 89% reduction in sz frequency
  - 18% reduce75-100%
  - 34% reduce 50-75%
  - 12% reduce 25-50%
  - 26% reduce <25%
- 7% pts aggravate sz -> CBD withdrawal

Tzadok et al, Seizure 2016 35:41-4

Ongoing & Future perspectives

- **CBD** as an adjunctive therapy for treatment resistant paediatric and adult epilepsies.
  - A number of phase III human trials underway
- **CBD-enriched cannabis** may have anti-seizure effects :
  - **Insufficient evidence of moderate/high quality studies** to assess whether there is a treatment effect of *Cannabis sativa, CBD:THC combinations or oral cannabis* extracts.
- **What is the right CBD:THC ratio?**

Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence : JNNP 2018;89:741–753

Research evidences on Cannabis & Cannabinoids in Rx of epilepsy

50% Reduction in Sz (19 studies , 2 RCTs)

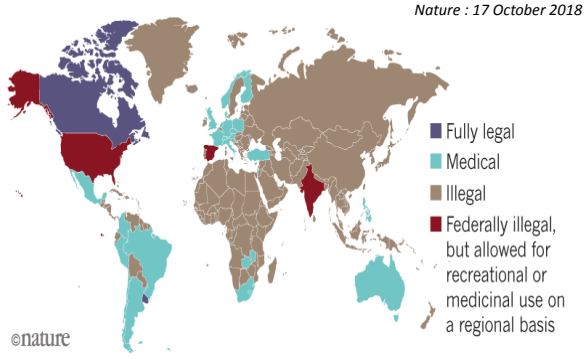
Cannabis sativa/extract	Two studies (no RCT)
Findings	Positive effect
Evidence GRADE	⊕◯◯◯ VERY LOW
Risk of bias	Serious to critical risk
Conclusion	Insufficient evidence
CBD	11 studies (2 RCT)
Findings	Small effect
Evidence GRADE	⊕⊕◯◯ LOW
Risk of bias	Low to serious risk
Conclusion	Some evidence of effect

CBD:THC	Five studies (no RCTs)
Findings	Positive effect
Evidence GRADE	⊕⊕◯◯ LOW
Risk of bias	Serious to critical risk
Conclusion	Insufficient evidence
Oral cannabis extracts	One study (no RCT)
Findings	Positive effect
Evidence GRADE	⊕◯◯◯ VERY LOW
Risk of bias	Critical risk
Conclusion	Insufficient evidence

JNNP 2018;89:741–753

Countries : legalized cannabis

Nature : 17 October 2018



Source: Arcview Market Research/BDS Analytics

ประเทศไทย พศ.2562

- โรคลมชักรักษายาก จัดอยู่ในกลุ่มข้อบ่งชี้ทางการแพทย์ ที่สามารถใช้ยาสกัดสารกัญชารักษาได้ตามกฎหมาย เนื่องจากมีข้อมูลทางวิชาการสนับสนุนผลการรักษาที่ได้ผลชัดเจน
- เมื่อมีการผลิตยาสกัดสารกัญชาตามมาตรฐานและนำมาใช้ ในประเทศไทย การติดตามการใช้ยาสกัดสารกัญชาอย่างใกล้ชิด คงต้องมีทั้งด้านผลการรักษา และผลข้างเคียง ทางคลินิก เพื่อเป็นข้อมูลที่สำคัญของประเทศต่อไป

ข้อแนะนำการใช้ยาสกัดกัญชา สำหรับโรคลมชัก

- พิจารณาใช้ในผู้ป่วยโรคลมชักรักษายาก คุมด้วยยากันชักมาตรฐานแล้วอย่างน้อย 2 ชนิดไม่ได้ผล
- เลือกยาที่มี CBD enriched
- ใช้แบบ adjuvant (ร่วมกับยากันชักอื่นๆ) และ ระวังเรื่อง drug interaction กับยากันชักและยาอื่นๆ
- เฝ้าระวังผลข้างเคียงที่สำคัญ คือ ภาวะตับอักเสบ ผลต่อจิตประสาท

ข้อควรระวังในการใช้ยาสกัดสารกัญชาในโรคลมชัก

- ไม่ใช้ในหญิงตั้งครรภ์
- ระวังในผู้ป่วยโรคตับ หรือ ระดับ liver enzyme ผิดปกติ
- ระวังในผู้ป่วยโรคจิตประสาทที่รุนแรง Schizophrenia, psychosis
- ระวังในผู้ที่มีข้อห้ามในการใช้ยากัญชา
- ระวังในผู้ที่เคยใช้กัญชามาก่อน (ที่ไม่ทราบขนาดของยา)

วิธีการใช้ยาสกัดสารกัญชาในโรคลมชัก

- ลงทะเบียนผู้ป่วยเพื่อขออนุมัติการใช้ยาสกัดกัญชาตามกฎหมาย
- แพทย์พิจารณาให้ยา ขนาด CBD 1-20 มก./กก./วัน และปรับตามอาการของผู้ป่วย โดยขนาดยาสุดท้าย ให้มี THC ไม่มากกว่า 0.5 มก./กก./วัน
- แพทย์ติดตามประเมินผลการรักษาและผลข้างเคียงของผู้ป่วย ในคลินิกอย่างน้อย 12 เดือน และรายงานผลให้กับศูนย์ติดตามการใช้ยาสกัดกัญชาตามกฎหมาย

Thank you